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**ATTN: TSCA Section 8(e) Submission**

Ref: 1. Four Week Oral Toxicity Study In The Rat With Two Week Recovery Period  
With [ ] (Interim Report), received July 24, 1995.

Dear Sirs:

In compliance with the reporting requirements of TSCA Section 8(e) Substantial Risk Information, we are submitting the enclosed Interim Study Report (Ref. 1.) for your review.

The interim report indicates the results of a four week rat oral toxicity study performed on the following R&D material currently being researched by [ ]:

Specific chemical name: Benzenebutanenitrile,  $\alpha,\alpha,\gamma$ -trimethyl  
Chemical Abstract Service number: 75490-39-0

The initial histopathological findings reported in the four week study indicate seminiferous tubular atrophy at the highest dose level. We will send any additional information, including the histopathological findings reported for lower dose levels, as soon as we receive it.

The material is currently in research, has not been manufactured or imported, and is not in commerce. We have informed our research department and the limited personnel associated with the research material regarding the results of this study. We have also added new information to the Material Safety Data Sheet to reflect these results. We will continue to advise the use of splash goggles or face shield when eye contact might occur, use of chemical resistant gloves, and use of a NIOSH approved respirator when inhalation of high concentrations may occur. The ventilation would meet ACGIH criteria.

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We have included sanitized and unsanitized versions of the Interim Study Report and request that you maintain our company identity, references to company personnel, and company synonyms and product codes of the chemical substance in this communication as "CONFIDENTIAL BUSINESS INFORMATION".

If you have any questions or comments, please contact me at [ ] .



[ ]

Enclosures



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Telephone: (01480) 890431 Facsimile: (01480) 890693

SAA/wt

19 July 1995

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Dear

**Re: Four week oral toxicity study in the rat with two week recovery period with  
(HRC Schedule Number)**

The experimentation for the above study has now been completed and a summary of the results is enclosed for your information.

The microscopic examinations are currently in progress and the histopathology results will be included in the draft report.

Yours sincerely

A handwritten signature in black ink, appearing to read "S A Allan".

Ms S A Allan BSc (Hons) CBiol MIBiol  
Study Director  
Department of Industrial Toxicology

A handwritten signature in black ink, appearing to read "D G Coleman".

Mr D G Coleman BSc (Hons)  
Study Supervisor  
Department of Industrial Toxicology



Interim report for the four week oral toxicity study with two week recovery period  
in the rat with (HRC Schedule Number)

The following report contains interim data (unaudited) generated up to the recovery sacrifice in the above study.

Treatment commenced on 25 April 1995 with a total of sixty rats allocated to groups as follows:

Group	Treatment	Dosage level (mg/kg/day)	No. of rats		Rat numbers	
			♂	♀	♂	♀
1	Control, corn oil	-	10	10	1-10	31-40
2		15	5	5	11-15	41-45
3		150	5	5	16-20	46-50
4		500	10	10	21-30	51-60

The appropriate concentration of the test substance, formulated as 3, 30 or 100 mg/ml solutions in corn oil, was administered by oral gavage, once daily to each rat of Groups 2 to 4 at a dose volume of 5 ml/kg/day for a minimum of 28 consecutive days. Control animals were treated in the same manner receiving the vehicle (corn oil) alone at the same dose volume (5 ml/kg/day) also by oral gavage.

Overnight urine samples were collected and blood was withdrawn under light ether anaesthesia from the orbital sinus of the five male and five female rats selected from Groups 1 and 4 and surviving rats of Groups 2 and 3. These samples were collected after 4 weeks of treatment (Day 30, 24 May 1995). Investigations were also carried out for remaining rats after the 2 week recovery period (Day 44, 7 June 1995) for all individual parameters statistically significantly different from control at Day 30. Blood and urine sampling, when undertaken at Day 44, followed a similar procedure to that carried out on Day 30.

Following the treatment period five male and five female rats from Groups 1 and 4 and all rats from Groups 2 and 3 were sacrificed on 26 May 1995. The remaining animals from Groups 1 and 4 were killed on 9 June 1995 following a two-week recovery period.

**RESULTS****MORTALITIES**

There were no treatment related mortalities.

One high dosage group female rat (No. 59) was found dead on Day 15. Clinical signs observed for the two days prior to death were hunched posture, pilo erection, cold to the touch, brown perianal staining and pallor of the extremities. Other incidental signs included increased salivation, wet coat, wet urogenital region and brown perioral staining. The post mortem macroscopic examination on this rat revealed a perforated oesophagus, thoracic cavity containing pale coagulum, congested lungs, enlarged adrenals and yellow/brown anogenital staining. Death was considered to be the result of a dosing error and not an effect of treatment.

One control male rat (No. 8) did not recover from the anaesthetic administered for the blood sampling procedure on Day 44. Death was considered to be the result of an anaesthetic accident.

There were no other mortalities.

**CLINICAL SIGNS**

There were no toxicologically important clinical signs noted throughout the study.

At 500 mg/kg/day (and to a lesser extent 150 mg/kg/day) increased salivation after dosing, sometimes accompanied by wet fur, was noted throughout the study. Salivation was accompanied by post-dose brown perioral staining on Day 5 for three rats (Nos. 16, 20 and 57). Increased salivation following dosing and associated signs (wet fur and brown perioral staining) are commonly observed in orally dosed rat studies and are considered to be as a result of unpalatability of the test substance and are therefore considered not to be of toxicological importance.

No other clinical signs were recorded for control or treated rats.

**BODYWEIGHT (Figure 1, Table 1)**

There were no statistically significant differences from control in bodyweight gains in any of the treatment groups recorded during the treatment or recovery periods.

During the recovery period the bodyweight gains for the high dosage male rats were 18% lower than control, however, as the actual difference in bodyweight gain was only 8 grams this difference was not considered to be related to treatment.



#### **FOOD CONSUMPTION (Figure 2, Table 2)**

The food consumption for high dosage group male and female rats was marginally higher than control on most occasions throughout the treatment and recovery periods. However, the difference from control is small and not considered to be toxicologically important.

The food consumption for male and female rats of the intermediate or low dosage groups over the treatment and recovery periods was similar to control.

#### **WATER CONSUMPTION (Figure 3, Table 3)**

The water consumption was measured by visual appraisal throughout the study and during Week 3 by gravimetric analysis following a suspected treatment related effect and again by gravimetric analysis during the second week of the recovery period to assess the reversibility of any effect seen during the treatment period.

##### **Week 3**

During Week 3 the water consumption was recorded to be higher than control for male (34% higher) and female (91% higher) rats receiving 500 mg/kg/day.

At Week 3 the water consumption for male and female rats in the remaining dosage groups (15 or 150 mg/kg/day) was similar to control.

##### **Week 2 Recovery**

During Week 2 Recovery the water consumption was higher than control for the high dosage group female rats (32% higher) and to a lesser extent for male rats (13% higher).

#### **HAEMATOLOGY (Table 4)**

There were no statistically significant differences from control that were considered to be related to treatment measured during the treatment or recovery periods.

##### **Week 5**

Higher than control monocyte counts were recorded for male rats receiving 500 mg/kg/day. However, as the difference from control was small and within the expected background range (Monocyte  $\times 10^3/\text{mm}^3$  rat ♀: 5 percentile 0.00, median 0.00, 95 percentile 0.16) an effect of treatment was considered unlikely.

##### **Week 3 Recovery**

There were no statistically significant differences from control measured during Week 3 Recovery.



## BIOCHEMISTRY (Table 5)

### Week 5

Statistically significantly higher than control globulin and hence total protein levels were recorded for female rats of the high dosage group. Consequently the A/G ratio for these rats was statistically significantly lower than control.

Statistically significantly lower than control alkaline phosphatase (AP) levels were recorded for female rats receiving 500 mg/kg/day. However there was wide variation within the groups.

There were no other statistically significant differences from control that were considered to be related to treatment measured during the treatment period.

Higher gamma-glutamyltransferase levels were recorded for some male rats treated at 500 mg/kg/day resulting in a slightly (but statistically significantly) higher than control mean value. However, this small difference from control was considered to have arisen by chance.

For female rats receiving 500 or 150 mg/kg/day the sodium ion concentration was statistically significantly higher than control. However, there was no dosage relationship and this small difference from control was not considered to be related to treatment.

Lower than control chloride ion concentrations were recorded for female rats receiving 500 mg/kg/day. The values were within the expected background range for rats of this age and strain (Cl mEq/l, rat ♀: 5 percentile 95, median 98 and 95 percentile 102). Therefore a treatment related effect was not suspected.

### Week 3 Recovery

There were no other statistically significant differences from control in any of the biochemical parameters measured at Week 3 Recovery.

## URINALYSIS (Table 6)

### Week 5

Lower than control urinary pH levels achieved statistical significance for female rats receiving 500 mg/kg/day.

There were no statistically significant differences from control in the urinalysis parameters measured during Week 5. Additionally, there were no differences from control that were considered to be treatment related for qualitative parameters measured.

### Week 3 Recovery

The urinary pH levels were statistically significantly lower than control for high dosage group female rats.



## ORGAN WEIGHTS (Table 7)

### Week 5

The liver weights (adjusted for bodyweight) for male and female rats receiving 500 or 150 mg/kg/day were statistically significantly higher than control.

There were no other differences from control in organ weights recorded for treated rats that were considered to be related to treatment.

In female rats receiving 500 mg/kg/day statistically significantly higher than control brain weights were recorded. There was substantial variation within the high dosage group and overlap between all the groups. As these values were within the expected background range for rats of this age and strain (Brain ♀ g: 5 percentile 1.7, median 1.8, 95 percentile 2.0), a treatment related effect was not suspected.

### Week 3 Recovery

Statistically significantly higher than control liver weights were recorded for female rats of the high dosage group. The importance of this finding may become clearer following histopathological examination.

Kidney weights (adjusted for bodyweight) for male and female rats were statistically significantly higher than control, the importance of this finding may become more clear following histopathological examination.

The prostate weight (bodyweight adjusted) was statistically significantly higher than control for male rats treated at 500 mg/kg/day. However, in the absence of any changes at Week 5 this is unlikely to be related to treatment.

No other statistically significantly differences from control were recorded in Week 3 recovery.

## MACROSCOPIC PATHOLOGY (Table 8)

### Termination

The macroscopic examinations performed at termination revealed the following changes attributable to treatment with

Enlargement of the liver was noted in 3/5 male rats and 3/5 female rats receiving 500 mg/kg/day and 1/5 male rats receiving 150 mg/kg/day compared with none in the control group.

Small testes in 3/5 male rats receiving 150 mg/kg/day and 2/5 male rats receiving 500 mg/kg/day compared with none in the control group.

### Recovery

The macroscopic examinations performed after a 2 week recovery period revealed the following change consistent with the terminal kill findings.

**HRC**

Small testes in 1/5 male rats receiving 500 mg/kg/day. Small testes were also seen in 1/4 rats in the control group, and the significance of this finding awaits histopathological examination.

#### **MICROSCOPIC PATHOLOGY**

Initial microscopic examination has revealed the following treatment-related changes in rats receiving 500 mg/kg/day.

- Liver      Centrilobular hepatocyte enlargement in both male and female rats.
- Kidneys    Cortical tubular eosinophilic inclusion in male rats only.
- Testes     Seminiferous tubular atrophy.

FIGURE 1

Bodyweights — group mean values

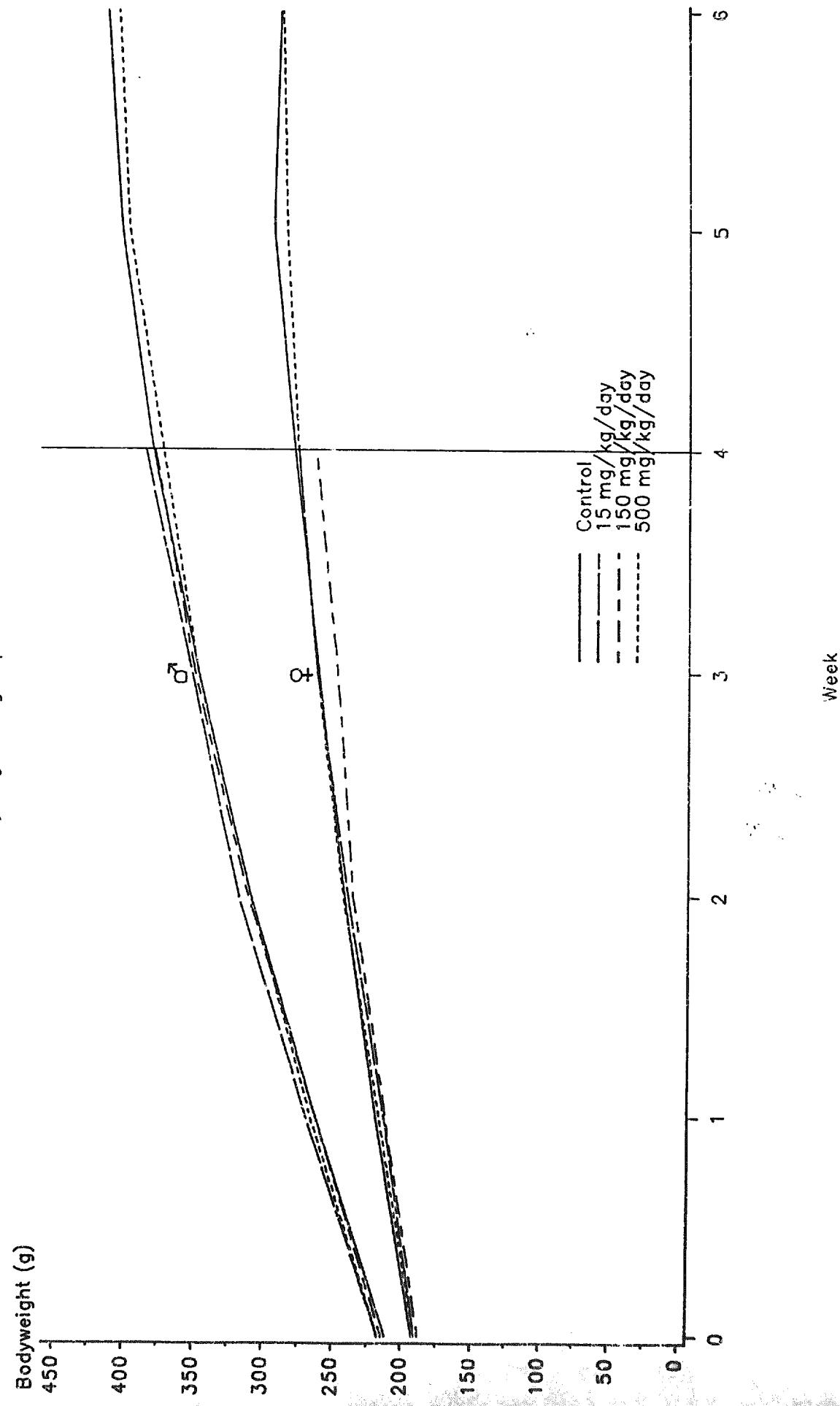


FIGURE 2

Food Consumption - group mean values

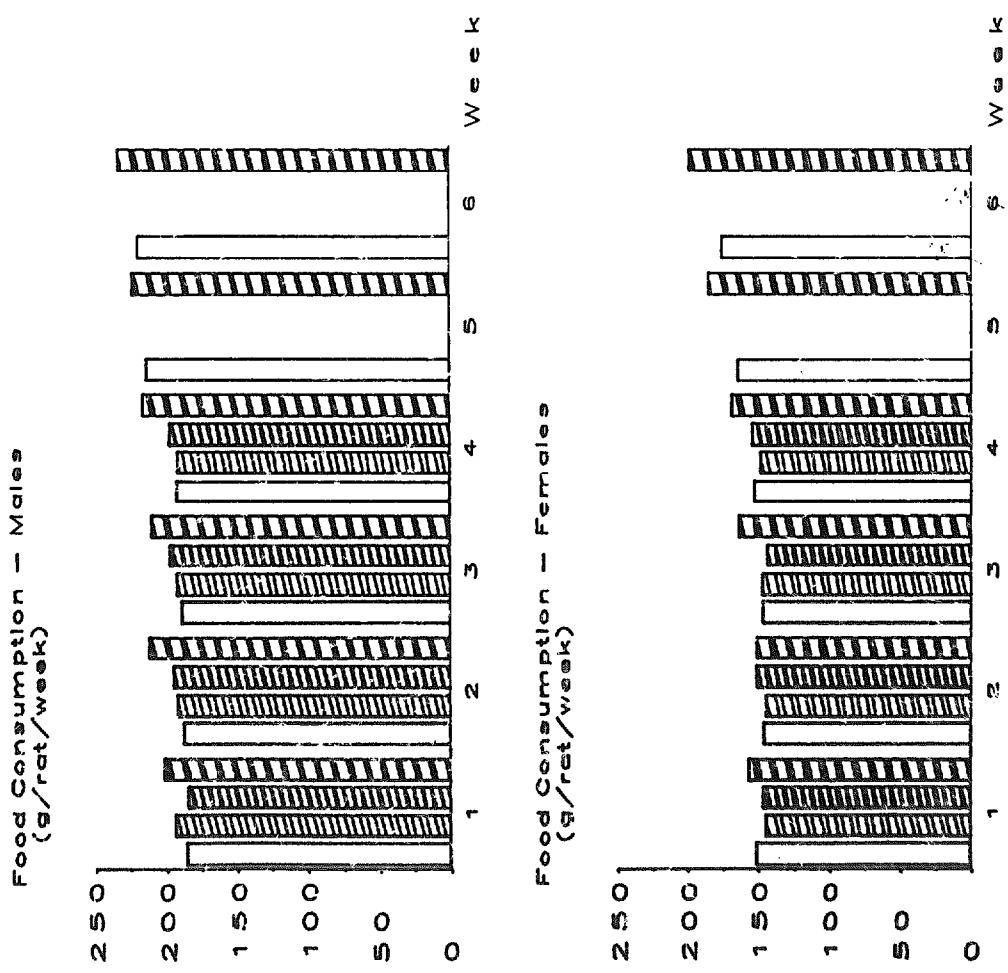


FIGURE 3

Water Consumption — group mean values

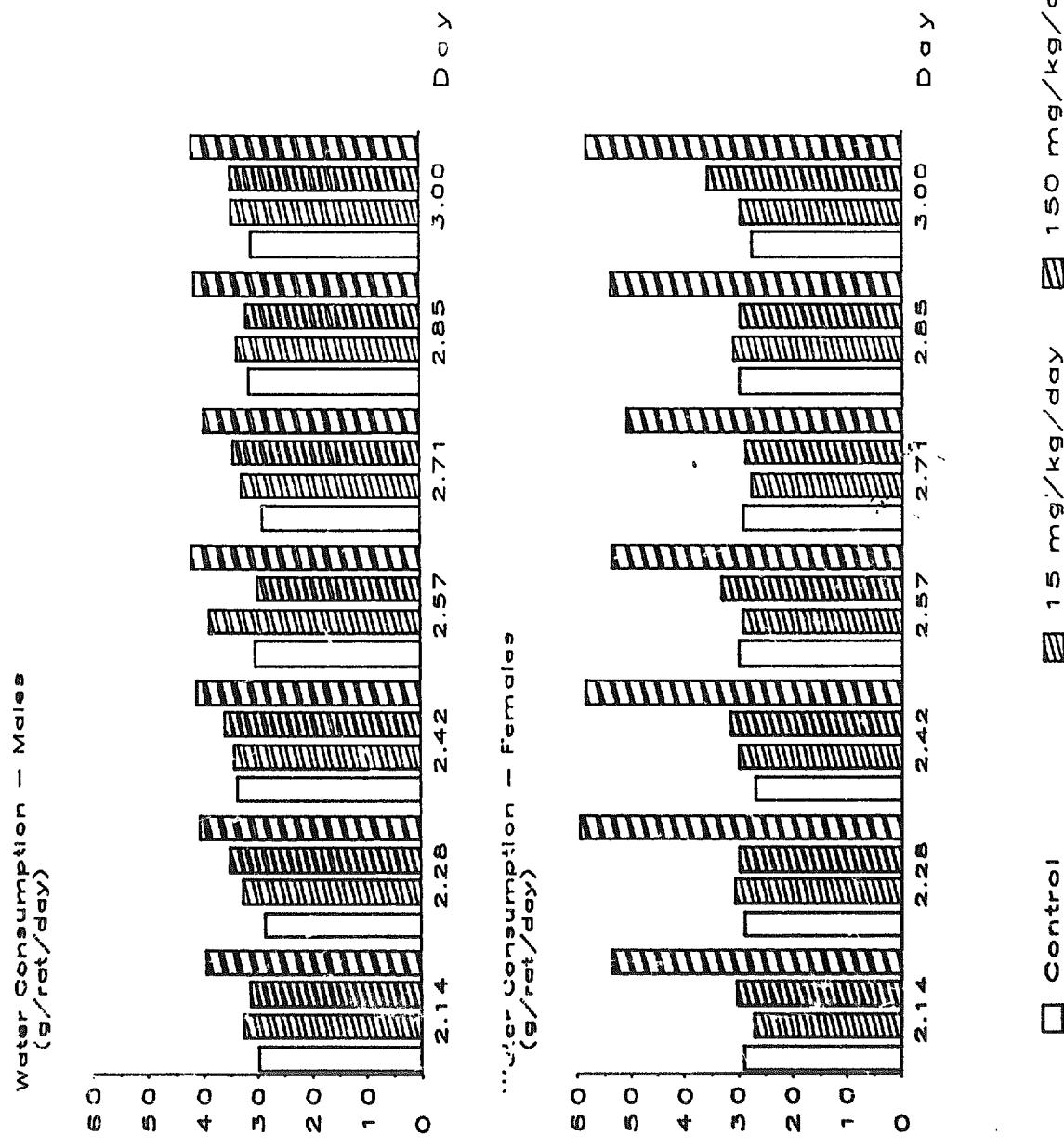


FIGURE 3

Water Consumption - group mean values

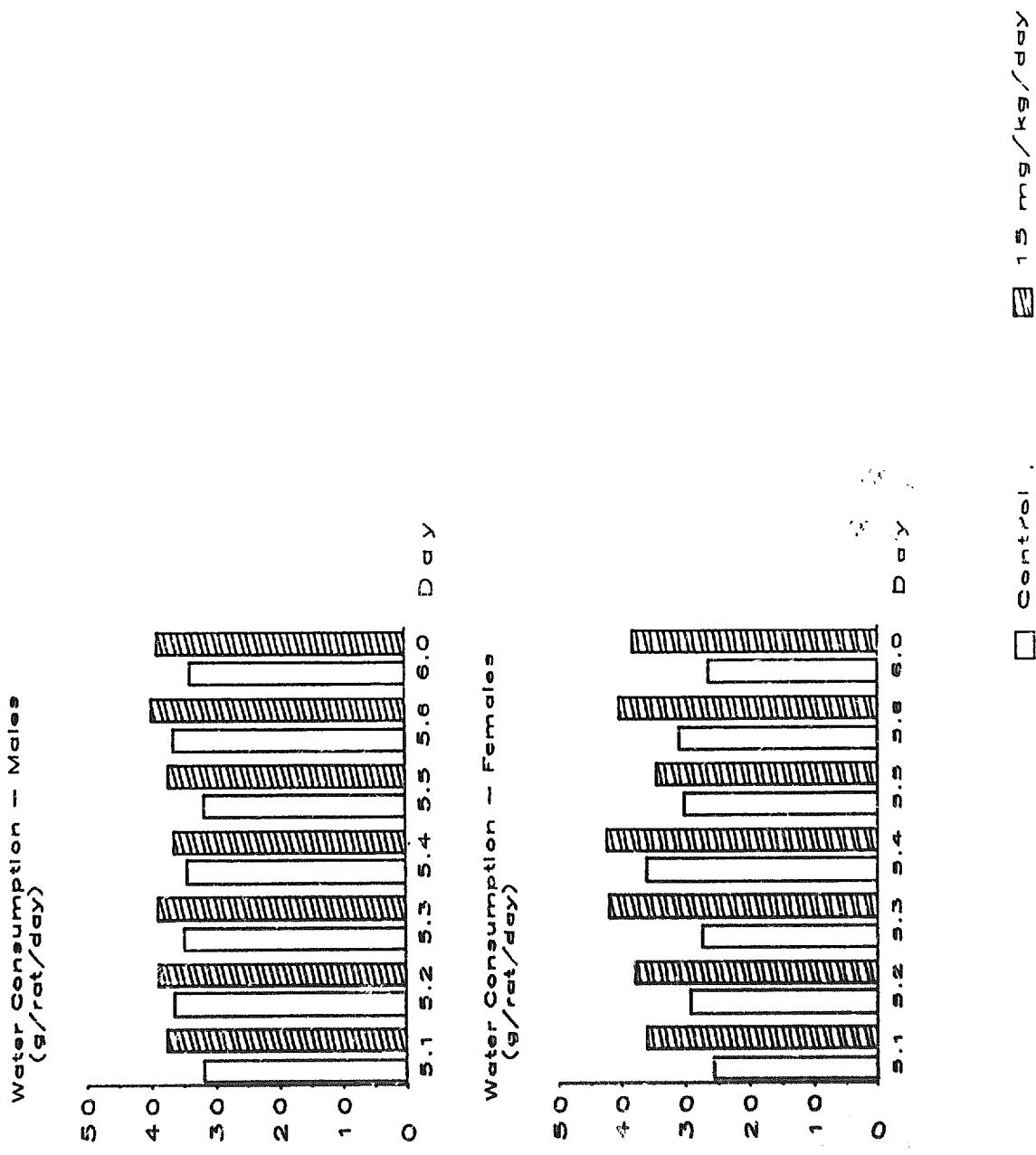


TABLE 1

## Bodyweights - group mean values (g)

Week	Group and dosage (mg/kg/day)								
	1m Control	2m 15	3m 150	4m 500	1f Control	2f 15	3f 150	4f 500	
<b>Dosing</b>									
0	212	217	214	217	193	190	188	191	
1	261	268	262	265	219	213	211	216	
2	307	316	309	307	241	238	235	242	
3	345	349	347	344	259	260	246	260	
4	378	383	376	370	277	275	262	274	
<b>Gain</b>									
Week 0-4	166	166	162	153	85	84	74	83	
% of Control Value	-	100	98	92	-	99	87	98	
<b>Recovery</b>									
0	374			373	279			278	
1	401			396	293			283	
2	413			405	288			287	
<b>Gain R0-R2</b>									
Week R0-R2	39			32	10			10	
% of Control Value	-			82	-			100	

No statistical significance ( $P<0.05$ ) for gain

TABLE 2

Food consumption - group mean values (g/rat/week)

Week	Group and dosage (mg/kg/day)							
	1m Control	2m 15	3m 150	4m 500	1f Control	2f 15	3f 150	4f 500
<b>Dosing</b>								
1	186	194	185	201	152	145	147	157
2	187	192	194	211	147	145	152	152
3	188	192	197	209	148	148	144	163
4	192	191	197	215	154	149	155	168
<b>Cumulative Value Week 0-4</b>								
	753	769	773	836	601	587	598	640
<b>% of Control Value</b>								
	-	102	103	111	-	98	100	106
<b>Recovery</b>								
1	212			223	165		185	
2	219			232	176		200	
<b>Cumulative Value Week R1-R2</b>								
	431			455	341		385	
<b>% of Control Value</b>								
	-			106	-		113	

Statistical analysis not performed as there was only one or two cages/sex/group

TABLE 3  
Water consumption - group mean values (g/rat/day)

Week	Group and dosage (mg/kg/day)							
	1m 3	2m 15	3m 150	4m 500	1f Control	2f 15	3f 150	4f 500
Day								
1	29.7	32.4	31.2	39.4	28.8	27.0	30.2	52.8
2	28.5	32.4	34.8	40.3	28.7	30.4	29.6	57.9
3	33.3	33.8	35.6	40.7	26.7	29.8	31.4	57.3
4	30.1	38.4	29.6	41.5	29.8	29.0	33.0	52.7
5	28.6	32.4	33.8	39.3	29.1	27.4	28.6	49.7
6	30.9	33.2	31.4	41.0	29.7	30.8	29.4	53.6
7	30.5	34.2	34.4	41.4	27.4	29.4	35.6	56.8
Cumulative Value Week 3	212	237	231	284	200	204	218	381
% of Control Value	-	112	109	134	-	102	109	191

No statistical analysis as there was only one or two cages/sex/group

## DRAFT REPORT : 34

TABLE 3

Water consumption - group mean values (g/rat/day)

Recovery		Group and dosage (mg/kg/day)			
Week		1m	4m	1f	4f
2	Control	500	Control	500	
<hr/>					
Day					
1	31.8	37.6	25.6	36.0	
2	36.4	38.8	29.2	37.8	
3	34.8	38.8	27.4	42.0	
4	34.2	36.2	36.0	42.3	
5	31.6	37.0	30.2	34.5	
6	36.2	39.6	31.0	40.3	
7	33.6	38.6	26.4	38.3	
<hr/>					
cumulative					
value	237	357	206	271	
Week R2					
<hr/>					
% of					
Control	-	113	-	132	
Value					
<hr/>					

No statistical analysis as there was only one cage/sex/group

TABLE 4  
Haematology - group mean values

## Week 5

Group/ dosage mg/kg/day	PCV %	Hb g/dl	RBC x10 <sup>6</sup> / mm <sup>3</sup>	MCHC %	MCV fl	Total	WBC + Diff x10 <sup>3</sup> /mm <sup>3</sup>					Plts x10 <sup>3</sup> / mm <sup>3</sup>	TT s	
							N	L	E	B	M			
1M Control	54	15.6	7.0	28.7	77	11.1	LT	2.12	8.80	0.06	0.00	0.13	668	23
2M 15	52	14.9	6.7	28.8	77	10.7	1.06	9.57	0.02	0.00	0.02	722	25	
3M 150	52	15.3	6.7	29.3	78	10.6	1.60	8.85	0.02	0.00	0.09	781	23	
4M 500	54	15.3	7.0	28.5	76	10.3	1.47	8.69	0.10	0.00	0.07	810	23	
1F Control	52	K 14.9	6.5	K 28.8	79	9.5	1.73	7.73	0.02	0.00	0.00	707	21	
2F 15	52	14.9	6.6	28.7	79	11.0	2.67	8.31	0.06	0.00	0.00	840	20	
3F 150	51	14.1	6.5	27.5	79	6.8	1.18	5.54	0.10	0.00	0.03	765	20	
4F 500	52	14.9	6.6	28.5	79	9.5	2.11	7.28	0.03	0.00	* 0.08	760	21	

\* P&lt;0.05 (Williams test)

LT Data log transformed

K Kruskal-Wallis analysis

NA No analysis necessary; all data values the same

TABLE 4

## Haematology - group mean values

## Week 3 Recovery

Group/ dosage	WBC + Diff x10 <sup>3</sup> /mm <sup>3</sup>					
mg/kg/day	Total	N	L	E	B	M
1F Control	9.3	2.24	6.94	0.07	0.00	0.04
4F 500	6.6	1.55	4.97	0.01	0.00	0.04

No statistical significance (P&gt;0.05)

TABLE 5  
Biochemistry - group mean values

## Week 5

Group/ dosage mg/kg/day	Glu- cose		Protein g/dl		A/G	Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml
	mg/dl	Total	Alb	Glob						
1M Control	127	6.3	2.9	3.4	0.87	11	0.5	328	29	50
2M 15	120	6.1	2.8	3.3	0.87	11	0.5	396	28	54
3M 150	130	6.3	2.9	3.4	0.86	11	0.5	293	23	49
4M 500	110	6.4	3.0	3.4	0.87	13	0.5	302	27	52
1F Control	137	6.5	3.1	3.4	0.91	13	0.5	238	31	53
2F 15	125	6.7	3.1	3.6	0.87	13	0.5	225	29	54
3F 150	122	6.7	3.2	3.5	0.92	13	0.5	183	26	47
4F 500	123	**	3.2	**	*	13	0.5	168	23	44

\* P<0.05, \*\* P<0.01 (Williams test)

TABLE 5  
(Biochemistry - continued)

Week 5										
Group/ dosage mg/kg/day	gGT mU/ ml	Bili- rubin mg/dl	Na mEq/ l	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl	Tri- glyc mg/dl	
1M Control	<1	<0.2	144	3.6	5.6	4.9	101	64	119	
2M 15	<1	0.1	144	3.7	5.7	4.7	100	59	111	
3M 150	<1	<0.2	144	3.8	5.6	4.9	100	63	94	
4M 500	*	1	0.2	145	3.9	5.7	4.8	100	66	89
1F Control	<1	0.1	143	3.7	5.7	4.1	102	56	63	
2F 15	<1	0.1	143	3.6	5.7	3.9	102	72	75	
3F 150	<1	0.2	145	3.3	5.7	4.0	102	66	57	
4F 500	1	0.2	144	3.6	5.9	3.9	99	71	75	

\* P&lt;0.05 (Williams test)

K Kruskal-Wallis analysis

TABLE 5

## Biochemistry - group mean values

## Week 3 Recovery

Group/ dosage mg/kg/day	Protein Total	g/dl	A/G	AP mU/ ml	gGT mU/ ml	Na mEq/ l	Cl mEq/ l
	Alb	Glob					
1M Control	-	-	-	-	-	<1	-
4M 500	-	-	-	-	-	<1	-
1F Control	7.2	3.0	4.3	0.70	159	-	144 103
4F 500	7.3	3.1	4.1	0.77	152	-	144 102

No statistical significance (P&gt;0.05)

- Parameter not recorded in this sex

TABLE 6  
Urinalysis - group mean values

Week 5		Vol. ume ml	pH	SG	Pro- tein mg/dL
Group/ dosage mg/kg/day					
1M	Control	4.8	6.2	1042	206
2M	15	5.4	6.1	1042	303
3M	150	5.3	6.5	1046	328
4M	500	6.5	6.1	1047	282
1F	Control	4.9	6.1	1041	68
2F	15	5.0	6.2	1035	64
3F	150	4.0	6.0	1040	80
4F	500	5.0	5.7	1046	71

\* P<0.05 (Williams test)

TABLE 6

Urinalysis - group mean values

Week 3 Recovery	
Group/ dosage mg/kg/day	pH
1F	
Control	6.5
4F	+
500	6.1

+ P<0.05 Student's t test

TABLE 7

Organ weights - group mean values

Week 5		Body wt		Brain		Liver		Spleen		Kidneys		Adrenals		Testes		Seminal Vesicle		Epididymides		Prostate	
Group/ dosage	mg/kg/day	g	g	g	g	g	g	g	g	g	g	g	g	L	R	g	g	g	g	g	g
<b>Unadjusted means</b>																					
1M Control		383	1.96	19.3	0.72	3.04		53.2	1.594	1.602	0.95	0.423	0.427	0.73							
2M 15		382	1.97	16.1	0.82	2.93		52.1	1.579	1.562	1.00	0.437	0.425	0.80							
3M 15C		377	1.88	21.8	0.72	3.16		52.5	1.454	1.335	0.96	0.401	0.363	0.74							
4M 500		362	1.88	25.4	0.72	3.25		54.2	1.483	1.448	1.01	0.408	0.424	0.77							
<b>Adjusted means</b>																					
1M	-	-	18.7	0.70	2.96		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2M	-	-	17.8	0.80	2.86		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3M	-	-	21.7	0.72	3.15		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4M	-	-	26.2	0.76	3.42		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

\* P&lt;0.05, \*\* P&lt;0.01 (Williams test)

TABLE 7

Organ weights - group mean values

Week 5		Group/ dosage mg/kg/day	Body wt g	Brain g	Liver g	Spleen g	Kidneys g	Adrenals mg	Ovaries mg
<b>Unadjusted means</b>									
1F	Control	275	1.95	12.3	0.65	2.38	70.2	97.9	
2F	15	273	1.89	12.7	0.68	2.21	77.6	100.3	
3F	150	262	1.88	13.1	0.64	2.24	74.3	96.0	
4F	500	269	1.82*	16.7	0.67	2.36	71.2	100.9	
<b>Adjusted means</b>									
1F	-	-	12.0	0.64	-	-	-	-	
2F	-	-	12.6	0.67	-	-	-	-	
3F	-	-	13.5	0.66	-	-	-	-	
4F	-	-	16.7	0.67	-	-	-	-	

\* P&lt;0.05, P&lt;0.01 (Williams test)

TABLE 7

Organ weights - group mean values

Week 3 Recovery												
Group/ dosage mg/kg/day	Body wt g	Brain g	Liver g	Spleen g	Kidneys g	Adrenals mg	Testes Left g	Testes Right g	Seminal Vesicle g	Epididymides Left g	Epididymides Right g	Prostate g
<b>Unadjusted means</b>												
1M	415	1.94	19.2	0.80	2.99	52.4	1.293	1.291	1.08	0.393	0.404	0.63
Control	407	1.98	22.0	0.82	3.42	60.0	1.543	1.505	1.17	0.467	0.465	0.89
4M	500	-	-	-	-	-	-	-	-	-	-	-
<b>Adjusted means</b>												
1M	-	-	-	-	2.94	-	-	-	-	-	-	-
4M	-	-	-	-	3.46++	-	-	-	-	-	-	-

+ P&lt;0.05, ++ P&lt;0.01 Student's t test

TABLE 7

## Organ weights - group mean values

Week 3 Recovery		Organ weights - group mean values					
Group/ dosage mg/kg/day	Body wt g	Brain g	Liver g	Spleen g	Kidneys g	Adrenals mg	Ovaries mg
<b>Unadjusted means</b>							
<sup>1</sup> F Control	289	1.96	12.7	0.66	2.31	75.9	92.9
<sup>4</sup> F 500	289	1.93	<sup>†</sup> 14.1	0.64	2.42	71.5	90.0

+ P&lt;0.05 Student's t test

TABLE 8

## PATHOLOGY - INTERGROUP COMPARISON OF MACROSCOPIC FINDINGS INCIDENCE

STUDY NO:	TITLE: TOXICITY TO RATS WITH									
	GROUP	GROUP	GROUP	GROUP	GROUP	GROUP	GROUP	GROUP	GROUP	GROUP
REMOVAL REASON: TERMINAL	1	2	3	4	1	2	1	2	3	4
	MALES					FEMALES				
ANIMALS ON STUDY	10	5	5	5	10	10	5	5	5	10
ANIMALS COMPLETED	5	5	5	5	5	5	5	5	5	5
FUR Stained.....	0	0	0	0	0	0	0	0	0	1
SKIN ALOPECIA Alopecia.....	0	0	0	0	0	0	1	0	0	0
LYMPH NODES - CERVICAL Enlarged.....	1	1	0	0	3	3	3	1	3	
LIVER Enlarged.....	0	0	1	2	0	0	0	0	0	3
TESTES Small.....	0	1	3	2	0	0	0	0	0	0
UTERUS Fluid distension.....	0	0	0	0	1	1	1	1	1	

TABLE 8  
STUDY NO: TITLE: TOXICITY TO RATS WITH  
PATHOLOGY - INTERGROUP COMPARISON OF MACROSCOPIC FINDINGS INCIDENCE

STUDY NO:	TITLE: TOXICITY TO RATS WITH		
	GROUP	GROUP	GROUP
REMOVAL REASON: RECOVERY	1	4	1
ANIMALS ON STUDY	10	10	10
ANIMALS COMPLETED	4	5	5
SKIN SCABS Scab/s... Atopicia: Atopicia:	0	0	0
LYMPH NODES - CERVICAL Enlarged.....	1	0	0
LUNGS Petechiae.....	1	2	5
KIDNEYS	0	1	0
STOMACH ANTRUM MUCOSA White nodule, near to limiting ridge..	0	0	0
KIDNEYS	0	0	0
Pale subcapsular area/s.....	0	0	1
Irregular cortical scarring.....	1	0	0
Misshepen.....	0	0	1
LYMPH NODES - LUMBAR Congested.....	0	0	1
Enlarged.....	0	0	1
TESTES small.... Blue....	1	1	0
			0

## APPENDIX 1

## Bodyweights - individual values (g)

## Group 1m Control

Cage number	Animal number	Week						
		0	1	2	3	4	R1	R2
1	1	221	266	304	343	378		
	2	234	290	339	376	413		
	3	215	266	318	356	393		
	4	187	245	298	332	364		
	5	211	255	292	323	358		
2	6	223	273	318	351	380	407	419
	7	201	249	301	345	385	416	428
	8	213	268	314	358	386	413	427
	9	215	260	305	345	373	394	407
	10	197	241	281	316	348	376	386

## R Recovery

## Group 2m 15 mg/kg/day

Cage number	Animal number	Week				
		0	1	2	3	4
3	11	215	267	310	349	386
	12	203	253	299	335	373
	13	220	269	323	343	368
	14	233	295	350	387	425
	15	214	257	296	332	362

## Group 3m 150 mg/kg/day

Cage number	Animal number	Week				
		0	1	2	3	4
4	16	204	246	290	324	351
	17	223	273	318	367	400
	18	202	246	293	329	353
	19	229	285	339	381	410
	20	213	258	305	334	367

## Group 4m 500 mg/kg/day

Cage number	Animal number	Week						
		0	1	2	3	4	R1	R2
5	21	216	284	324	357	378		
	22	234	255	300	337	362		
	23	203	250	287	319	342		
	24	222	269	316	359	390		
	25	211	256	299	334	364		
6	26	236	288	325	356	379	402	402
	27	212	256	284	315	336	350	360
	28	219	272	314	354	386	414	427
	29	215	273	325	368	398	422	433
	30	200	246	296	345	366	391	402

## R Recovery

## APPENDIX 1

(Bodyweights - continued)

## Group 1f Control

Cage number	Animal number	Week						
		0	1	2	3	4	R1	R2
7	31	203	231	260	271	294		
	32	203	238	272	298	311		
	33	192	209	221	244	261		
	34	173	189	209	225	241		
	35	188	210	231	253	269		
8	36	201	229	252	263	290	308	305
	37	200	228	256	275	293	296	293
	38	193	221	233	264	283	297	288
	39	192	220	242	248	264	285	279
	40	180	211	234	251	264	277	277

## R Recovery

## Group 2f 15 mg/kg/day

Cage number	Animal number	Week				
		0	1	2	3	4
9	41	190	207	227	242	261
	42	176	196	221	247	253
	43	199	226	260	277	295
	44	198	221	242	269	281
	45	189	213	242	267	283

## Group 3f 150 mg/kg/day

Cage number	Animal number	Week				
		0	1	2	3	4
10	46	182	201	221	213	242
	47	184	195	220	228	238
	48	188	217	244	275	296
	49	201	230	256	270	280
	50	185	214	232	242	253

## Group 4f 500 mg/kg/day

Cage number	Animal number	Week						
		0	1	2	3	4	R1	R2
11	51	205	213	268	293	309		
	52	185	238	235	251	269		
	53	171	193	209	227	245		
	54	195	220	242	263	266		
	55	194	219	241	255	268		
12	56	199	212	245	262	274	280	286
	57	194	224	240	257	268	266	274
	58	199	222	253	267	291	300	296
	59	183	210					
	60	181	208	241	268	278	287	293

## R Recovery

## APPENDIX 2

Food consumption - cage mean values (g/rat/week)

Group 1m Control			Group 2m 15		
Week	Cage		Week.	Cage	
	1	2		3	
Dosing			Dosing		
1	186	186	1	194	
2	184	190	2	192	
3	183	194	3	192	
4	188	196	4	191	
Recovery					
1		212			
2		219			

Group 3m 150			Group 4m 500		
Week	Cage		Week	Cage	
	4			5	6
Dosing			Dosing		
1	185		1	192	211
2	194		2	203	219
3	197		3	199	219
4	197		4	203	228
Recovery					
1				223	
2				232	

Group 1f Control			Group 2f 15		
Week	Cage		Week	Cage	
	7	8		9	
Dosing			Dosing		
1	149	154	1	145	
2	146	147	2	145	
3	148	147	3	148	
4	152	156	4	149	
Recovery					
1		165			
2		176			

Group 3f 150			Group 4f 500		
Week	Cage		Week	Cage	
	10			11	12
Dosing			Dosing		
1	147		1	150	164
2	152		2	152	152
3	144		3	152	176
4	155		4	164	174
Recovery					
1				185	
2				200	

## DRAFT REPORT : 35

## APPENDIX 3

Water consumption - cage mean values (g/rat/day)

Group 1m  
Control

Week	Cage	
	3	2
Day	1	28.8
	2	29.0
	3	31.0
	4	29.8
	5	27.0
	6	29.6
	7	29.0

Group 2m  
15

Week	Cage	
	3	3
Day	1	32.4
	2	32.4
	3	33.8
	4	38.4
	5	32.4
	6	33.2
	7	34.2

Group 3m  
150

Week	Cage	
	3	4
Day	1	31.2
	2	34.8
	3	35.6
	4	29.6
	5	33.8
	6	31.4
	7	34.4

Group 4m  
500

Week	Cage	
	3	5
Day	1	39.0
	2	39.8
	3	39.6
	4	42.4
	5	38.0
	6	41.0
	7	41.0

Group 1f  
Control

Week	Cage	
	3	7
Day	1	28.6
	2	31.2
	3	26.6
	4	32.6
	5	28.4
	6	34.2
	7	28.0

Group 2f  
15

Week	Cage	
	3	9
Day	1	27.0
	2	30.4
	3	29.8
	4	29.0
	5	27.4
	6	30.8
	7	29.4

Group 3f  
150

Week	Cage	
	3	10
Day	1	30.2
	2	29.6
	3	31.4
	4	33.0
	5	28.6
	6	29.4
	7	35.6

Group 4f  
500

Week	Cage	
	3	11
Day	1	47.0
	2	46.0
	3	49.2
	4	46.4
	5	42.4
	6	52.8
	7	45.4

## APPENDIX 4

## Haematology - individual values

Week 5 (24 May 1995)

Group/ dosage mg/kg/day	Animal no.	PCV	Hb	RBC	MCHC	MCV	WBC + Diff x103/mm <sup>3</sup>						Plts	TT	
		%	g/dl	x106/ mm <sup>3</sup>	%	fL	Total	N	L	E	B	M	x103/ mm <sup>3</sup>	s	
Control	1m	55	15.8	7.1	28.7	77	11.3	2.49	8.70	0.00	0.00	0.11	688	24	
	2	53	15.1	6.9	28.5	77	15.1	2.27	12.38	0.00	0.00	0.45	690	22	
	3	54	15.6	7.0	28.9	77	9.0	0.72	8.28	0.00	0.00	0.00	734	24	
	4 P	56	16.3	7.2	29.1	78	9.3	3.07	6.05	0.09	0.00	0.09	633	24	
	5	54	15.3	7.0	28.3	77	10.9	2.07	8.61	0.22	0.00	0.00	593	23	
15	Mean	54	15.6	7.0	28.7	77	11.1	2.12	8.80	0.06	0.00	0.13	668	23	
	sd	1.1	0.47	0.11	0.32	0.4	2.44	0.870	2.275	0.097	0.000	0.186	55.0	0.9	
	2m	11 P	51	15.1	6.6	29.6	77	11.2	1.12	10.08	0.00	0.00	0.00	428	22
	15	12 P	50	14.6	6.4	29.2	78	8.4	0.92	7.39	0.08	0.00	0.00	769	25
	13	52	14.6	6.6	28.1	79	13.5	0.58	12.83	0.00	0.00	0.00	880	24	
150	14 PA	54	15.3	7.0	28.3	77	9.4	0.94	8.46	0.00	0.00	0.00	735	26	
	15	52	15.1	6.8	29.0	76	10.8	1.62	9.07	0.00	0.00	0.11	797	26	
	Mean	52	14.9	6.7	28.8	77	10.7	1.06	9.57	0.02	0.00	0.02	722	25	
	sd	1.5	0.32	0.23	0.63	1.1	1.94	0.352	2.069	0.036	0.000	0.049	172.8	1.8	
	3m	16	54	15.9	7.1	29.4	76	9.5	1.81	7.60	0.00	0.00	0.10	830	25
500	17	49	14.8	6.4	30.2	77	15.5	3.10	12.40	0.00	0.00	0.00	711	23	
	18 P	52	15.1	6.6	29.0	79	9.4	1.41	7.71	0.09	0.00	0.19	719	22	
	19 PA	54	15.4	6.8	28.5	79	10.3	1.03	9.17	0.00	0.00	0.10	838	23	
	20 PA	53	15.5	6.8	29.2	78	8.1	0.65	7.37	0.00	0.00	0.08	808	21	
	Mean	52	15.3	6.7	29.3	78	10.6	1.60	8.85	0.02	0.00	0.09	781	23	
4m	sd	2.1	0.42	0.26	0.62	1.3	2.87	0.943	2.107	0.040	0.000	0.068	61.5	1.5	
	21	55	15.1	7.2	27.5	76	12.4	1.61	10.54	0.12	0.00	0.12	913	23	
	22	55	15.9	7.3	28.9	75	8.7	1.57	6.87	0.26	0.00	0.00	732	23	
	23 P	54	15.4	6.8	28.5	79	9.8	1.37	8.33	0.10	0.00	0.00	818	21	
	24	51	14.9	6.8	29.2	75	10.8	1.51	9.18	0.00	0.00	0.11	831	23	
500	25 PA	54	15.4	7.0	28.5	77	9.9	1.29	8.51	0.00	0.00	0.10	756	24	
	Mean	54	15.3	7.0	28.5	76	10.3	1.47	8.69	0.10	0.00	0.07	810	23	
	sd	1.6	0.38	0.23	0.64	1.7	1.38	0.136	1.336	0.107	0.000	0.061	70.9	1.2	

sd Standard deviation

P Slight polychromasia

A Slight anisocytosis

## APPENDIX 4

(Haematology - continued)

Week 5 (24 May 1995)

Group/ dosage mg/kg/day	Animal no.	PCV	Hb	RBC	MCHC	MCV	WBC + Diff x103/mm <sup>3</sup>					Plts	TT	
		%	g/dl	x106/ mm <sup>3</sup>	%	fL	Total	N	L	E	B	M	x103/ mm <sup>3</sup>	s
1f Control	31 A	51	14.9	6.3	29.2	81	10.4	2.60	7.80	0.00	0.00	0.00	738	19
	32 PA	51	14.9	6.2	29.2	82	11.0	2.53	8.47	0.00	0.00	0.00	824	22
	33	51	14.7	6.5	28.8	78	7.5	0.45	7.05	0.00	0.00	0.00	696	23
	34 PA	52	14.9	6.6	28.7	79	9.2	1.56	7.54	0.09	0.00	0.00	701	20
	35 PA	53	14.9	6.9	28.1	77	9.3	1.49	7.81	0.00	0.00	0.00	574	CTD
	Mean	52	14.9	6.5	28.8	79	9.5	1.73	7.73	0.02	0.00	0.00	707	21
2f 15	sd	0.9	0.09	0.27	0.45	2.1	1.34	0.883	0.514	0.040	0.000	0.000	90.1	1.8
	41	52	14.4	6.7	27.7	78	11.2	2.58	8.51	0.11	0.00	0.00	702	19
	42	54	15.2	6.9	28.1	78	13.3	3.99	9.31	0.00	0.00	0.00	607	20
	43 PA	50	14.7	6.3	29.4	79	12.7	3.56	9.14	0.00	0.00	0.00	1070	22
	44 A	53	15.2	6.6	28.7	80	9.1	1.37	7.55	0.18	0.00	0.00	975	21
	45 A	51	15.0	6.5	29.4	78	8.9	1.87	7.03	0.00	0.00	0.00	846	19
3f 150	Mean	52	14.9	6.6	28.7	79	11.0	2.67	8.31	0.06	0.00	0.00	840	20
	sd	1.6	0.35	0.22	0.76	0.9	2.01	1.104	0.993	0.083	0.000	0.000	190.1	1.3
	46	51	14.2	6.7	27.8	76	6.0	2.64	3.30	0.06	0.00	0.00	674	18
	47 A	53	15.0	6.7	28.3	79	7.7	1.00	6.47	0.15	0.00	0.08	955	20
	48 PA	49	12.1	6.1	24.7	80	5.5	0.83	4.62	0.00	0.00	0.06	788	21
	49	51	14.6	6.4	28.6	80	7.3	0.88	6.13	0.29	0.00	0.00	794	20
4f 500	50 A	52	14.7	6.4	28.3	81	7.7	0.54	7.16	0.00	0.00	0.00	612	20
	Mean	51	14.1	6.5	27.5	79	6.8	1.18	5.54	0.10	0.00	0.03	765	20
	sd	1.5	1.16	0.25	1.61	1.9	1.02	0.835	1.557	0.123	0.000	0.039	131.5	1.1
	51	54	15.2	6.9	28.1	78	10.4	2.29	7.90	0.10	0.00	0.10	760	22
	52 A	53	15.0	6.7	28.3	79	10.7	2.14	8.35	0.00	0.00	0.21	873	CTD
	53 PA	52	14.8	6.4	28.5	81	12.7	4.70	8.00	0.00	0.00	0.00	620	CTD
500	54 A	50	14.3	6.5	28.6	77	5.5	0.83	4.51	0.06	0.00	0.11	780	21
	55 PA	52	15.0	6.6	28.8	79	8.2	0.57	7.63	0.00	0.00	0.00	765	20
	Mean	52	14.9	6.6	28.5	79	9.5	2.11	7.28	0.03	0.00	0.08	760	21
	sd	1.5	0.34	0.19	0.27	1.5	2.75	1.639	1.569	0.046	0.000	0.088	90.5	0.7

sd Standard deviation

CTD Clotted Sample

P Slight polychromasia

A Slight anisocytosis

## APPENDIX 4

## (Haematology - continued)

## Week 3 Recovery (7 June 1995)

Group/ dosage mg/kg/day	Animal no.	WBC + Diff x10 <sup>3</sup> /mm <sup>3</sup>					
		Total	N	L	E	B	M
Control	1f 36	8.8	2.29	6.34	0.09	0.00	0.09
	37	12.8	2.94	9.86	0.00	0.00	0.00
	38	5.7	1.31	4.33	0.06	0.00	0.00
	39	9.1	2.55	6.28	0.18	0.00	0.09
	40	10.0	2.10	7.90	0.00	0.00	0.00
Mean		9.3	2.24	6.94	0.07	0.00	0.04
sd		2.55	0.607	2.065	0.075	0.000	0.049
500	4f 56	6.5	1.56	4.88	0.00	0.00	0.07
	57	4.9	0.69	4.17	0.05	0.00	0.00
	58	7.5	2.18	5.33	0.00	0.00	0.00
	60	7.3	1.75	5.48	0.00	0.00	0.07
	Mean	6.6	1.55	4.97	0.01	0.00	0.04
sd		1.18	0.626	0.588	0.025	0.000	0.040

sd Standard deviation

## APPENDIX 5

## Biochemistry - individual values

Week 5 (24 May 1995)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl	A/G	Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml
		Total	Alb Glob						
1m Control	1	109	6.7	2.7	4.0	0.68	10	0.5	293
	2	144	5.8	2.7	3.1	0.87	14	0.5	370
	3	119	6.3	2.9	3.4	0.85	8	0.5	318
	4	141	6.4	3.2	3.2	1.00	10	0.5	261
	5	121	6.3	3.1	3.2	0.97	11	0.5	400
Mean		127	6.3	2.9	3.4	0.87	11	0.5	328
sd		15.1	0.32	0.23	0.36	0.126	2.2	0.00	56.5
								3.2	8.3
2m 15	11	131	6.0	2.7	3.3	0.82	11	0.5	371
	12	106	6.2	3.0	3.2	0.94	11	0.5	503
	13	130	5.8	2.8	3.0	0.93	10	0.6	222
	14	122	6.2	2.8	3.4	0.82	12	0.6	419
	15	110	6.3	2.9	3.4	0.85	10	0.4	467
Mean		120	6.1	2.8	3.3	0.87	11	0.5	396
sd		11.4	0.20	0.11	0.17	0.059	0.8	0.08	109.5
								6.2	9.6
3m 150	16	130	6.1	3.0	3.1	0.97	12	0.6	282
	17	154	6.2	2.7	3.5	0.77	14	0.5	324
	18	112	6.4	2.9	3.5	0.83	9	0.5	192
	19	140	6.4	2.9	3.5	0.83	10	0.5	298
	20	115	6.2	2.9	3.3	0.88	12	0.5	370
Mean		130	6.3	2.9	3.4	0.86	11	0.5	293
sd		17.5	0.13	0.11	0.18	0.075	1.9	0.04	65.6
								1.8	7.0
4m 500	21	117	6.5	3.0	3.5	0.86	10	0.5	253
	22	106	6.8	3.0	3.8	0.79	17	0.5	346
	23	111	6.3	3.1	3.2	0.97	13	0.5	333
	24	97	6.0	2.9	3.1	0.94	11	0.5	251
	25	118	6.5	2.9	3.6	0.81	12	0.4	326
Mean		110	6.4	3.0	3.4	0.87	13	0.5	302
sd		8.6	0.29	0.08	0.29	0.079	2.7	0.04	46.0
								6.3	5.1

sd Standard deviation

## APPENDIX 5

## (Biochemistry - continued)

Week 5 (24 May 1995)

Group/ dosage mg/kg/day	Animal no.	gGT	Bili- rubin	Na	K	Ca	P	Cl	Chol	Tri- glyc	
		mU/ ml	mEq/ mg/dl	mEq/ l	mEq/ l	mEq/ l	mEq/ l	mEq/ l	mg/dl	mg/dl	
1m Control	1	1	0.2	144	3.7	5.9	4.7	101	83	109	
	2	<1	0.1	145	3.7	5.3	5.7	100	50	112	
	3	1	<0.1	145	3.2	5.7	4.6	101	56	99	
	4	<1	0.1	144	3.9	5.5	4.6	100	65	INS	
	5	<1	0.1	144	3.6	5.7	4.9	101	64	157	
Mean		<1	<0.2	144	3.6	5.6	4.9	101	64	119	
sd				0.5	0.26	0.23	0.46	0.5	12.5	25.8	
2m 15	11	1	0.1	144	4.2	5.7	4.3	101	75	114	
	12	1	0.1	144	3.4	5.7	4.8	100	59	128	
	13	1	0.1	144	3.4	5.7	5.2	99	46	60	
	14	<1	0.2	144	3.6	5.8	4.5	102	53	136	
	15	<1	0.1	142	3.7	5.7	4.6	100	62	119	
Mean		<1	0.1	144	3.7	5.7	4.7	100	59	111	
sd				0.04	0.9	0.33	0.04	0.34	1.1	10.8	29.9
3m 150	16	<1	<0.1	143	3.9	5.5	4.9	100	38	79	
	17	1	0.1	144	4.0	5.6	5.3	101	80	132	
	18	<1	0.1	145	3.7	5.8	4.9	101	61	93	
	19	1	0.2	143	3.7	5.7	4.8	99	63	83	
	20	<1	0.2	145	3.5	5.4	4.5	101	74	78	
Mean		<1	<0.2	144	3.8	5.6	4.9	100	63	94	
sd				1.0	0.19	0.16	0.29	0.9	16.1	22.1	
4m 500	21	2	0.1	144	3.8	5.7	4.1	101	59	99	
	22	1	0.2	145	3.9	5.7	5.4	98	46	107	
	23	1	0.2	144	4.4	5.6	4.2	100	94	64	
	24	1	0.1	146	3.8	5.8	5.3	100	79	113	
	25	1	0.2	144	3.8	5.7	4.8	99	50	62	
Mean		1	0.2	145	3.9	5.7	4.8	100	66	89	
sd		0.4	0.05	0.9	0.26	0.07	0.60	1.1	20.4	24.3	

sd Standard deviation

## APPENDIX 5

(Biochemistry - continued)

Week 5 (24 May 1995)

Group/ dosage mg/kg/day	Animal no.	Glu- cose mg/dl	Protein g/dl	A/G	Urea Nitr mg/dl	Creat- inine mg/dl	AP mU/ ml	GPT mU/ ml	GOT mU/ ml
		mg/dl	Total	Alb Glob					
1f Control	31	128	7.0	3.1	3.9	0.79	16	0.5	239
	32	147	6.7	3.0	3.7	0.81	12	0.4	300
	33	151	6.1	3.1	3.0	1.03	11	0.5	223
	34	147	6.3	3.1	3.2	0.97	14	0.5	177
	35	114	6.6	3.2	3.4	0.94	12	0.4	253
Mean		137	6.5	3.1	3.4	0.91	13	0.5	238
sd		15.9	0.35	0.07	0.36	0.104	2.0	0.05	44.8
									7.0
2f 15	41	132	6.6	2.9	3.7	0.78	12	0.4	253
	42	116	7.0	3.2	3.8	0.84	14	0.4	233
	43	129	6.7	3.1	3.6	0.86	13	0.5	281
	44	133	6.4	3.0	3.4	0.98	11	0.5	225
	45	115	6.7	3.3	3.4	0.97	13	0.5	135
Mean		125	6.7	3.1	3.6	0.87	13	0.5	225
sd		8.8	0.22	0.16	0.18	0.069	1.1	0.05	55.0
									6.6
									10.0
3f 150	46	120	6.9	3.3	3.6	0.92	13	0.6	150
	47	105	6.6	3.3	3.3	1.00	11	0.5	165
	48	134	6.7	3.1	3.6	0.86	12	0.5	220
	49	134	6.6	3.2	3.4	0.94	15	0.5	209
	50	119	6.6	3.1	3.5	0.89	12	0.5	170
Mean		122	6.7	3.2	3.5	0.92	13	0.5	183
sd		12.1	0.13	0.10	0.13	0.053	1.5	0.04	30.1
									3.8
									4.3
4f 500	51	134	7.3	3.2	4.1	0.78	12	0.5	197
	52	120	7.0	3.1	3.9	0.79	15	0.6	214
	53	89	7.5	3.2	4.3	0.74	12	0.4	158
	54	147	6.8	3.1	3.7	0.84	14	0.6	153
	55	124	7.3	3.3	4.0	0.83	12	0.4	116
Mean		123	7.2	3.2	4.0	0.80	13	0.5	168
sd		21.6	0.28	0.08	0.22	0.040	1.4	0.10	38.7
									3.7
									6.9

sd Standard deviation

## APPENDIX 5

(Biochemistry - continued)

Week 5 (24 May 1995)

Group/ dosage mg/kg/day	Animal no.	gGT	Bili:- mU/	Na mEq/ ml	K mEq/ l	Ca mEq/ l	P mEq/ l	Cl mEq/ l	Chol mg/dl	Tri- glyc mg/dl
Control	31	<1	0.1	143	3.5	5.7	3.9	102	57	60
	32	1	0.2	142	3.9	5.8	4.1	101	62	92
	33	<1	0.1	144	4.0	5.5	4.2	104	55	48
	34	1	0.1	142	3.5	5.7	4.2	101	53	62
	35	1	0.2	144	3.6	5.9	4.2	102	53	52
Mean		<1	0.1	143	3.7	5.7	4.1	102	56	63
sd			0.05	1.0	0.23	0.15	0.13	1.2	3.7	17.3
15	41	1	0.1	144	3.6	5.7	4.1	102	69	64
	42	<1	0.2	142	3.6	5.9	4.0	102	64	59
	43	1	0.1	142	3.5	5.6	3.8	101	77	104
	44	1	0.1	144	3.4	5.6	3.6	101	84	104
	45	<1	0.2	144	3.7	5.7	3.9	102	68	43
Mean		<1	0.1	143	3.6	5.7	3.9	102	72	75
sd			0.05	1.1	0.11	0.12	0.19	0.5	8.0	27.8
150	46	1	0.2	145	3.1	5.6	3.8	102	48	37
	47	<1	0.1	147	3.3	5.8	3.7	104	74	47
	48	<1	0.1	144	3.4	5.6	3.7	101	77	59
	49	<1	0.2	146	3.2	5.9	4.7	102	65	88
	50	1	0.3	145	3.4	5.8	3.9	103	65	55
Mean		<1	0.2	145	3.3	5.7	4.0	102	66	57
sd			0.08	1.1	0.13	0.13	0.42	1.1	11.3	19.2
500	51	1	0.1	145	3.4	5.8	3.7	99	47	83
	52	1	0.1	145	3.5	5.9	3.9	101	54	79
	53	3	0.2	145	3.5	5.9	3.6	99	111	70
	54	1	0.1	144	3.6	5.8	4.5	100	43	63
	55	1	0.4	143	4.1	6.0	4.0	98	102	81
Mean		1	0.2	144	3.6	5.9	3.9	99	71	75
sd		0.9	0.13	0.9	0.28	0.08	0.35	1.1	32.4	8.4

sd Standard deviation

## APPENDIX 5

## Biochemistry - individual values

## Week 3 Recovery (7 June 1995)

Group/ dosage mg/kg/day	Animal no.	gGT mU/ ml
Control	6	<1
	7	<1
	8	<1
	9	<1
	10	<1
Mean		<1
sd		
4m 500	26	<1
	27	<1
	28	1
	29	<1
	30	<1
Mean		<1
sd		

sd Standard deviation

## APPENDIX 5

## (Biochemistry - continued)

## Week 3 Recovery (7 June 1995)

Group/ dosage mg/kg/day	Animal no.	Protein g/dl		A/G	AP mU/ ml	Na mEq/ l	Cl mEq/ l		
		Total	Alb Glob						
Control	1f	36	7.1	2.7	4.4	0.61	213	142	102
	37	7.0	3.0	4.0	0.75	218	144	103	
	38	7.6	3.0	4.6	0.65	135	144	101	
	39	7.6	3.2	4.4	0.73	107	145	105	
	40	6.9	3.0	3.9	0.77	121	144	105	
Mean		7.2	3.0	4.3	0.70	159	144	103	
sd		0.34	0.18	0.30	0.069	52.7	1.1	1.8	
500	4f	56	7.5	3.6	3.9	0.92	129	145	101
	57	6.9	3.2	3.7	0.86	149	145	102	
	58	7.3	2.8	4.5	0.62	174	142	101	
	60	7.3	2.9	4.4	0.66	155	144	103	
	Mean	7.3	3.1	4.1	0.77	152	144	102	
sd		0.25	0.36	0.39	0.147	18.5	1.4	1.0	

sd Standard deviation

## Organ weights - individual values

Week 3 Recovery (9 June 1995)

	Animal no.	Body wt	Brain g	Liver g	Spleen g	Kidneys g	Adrenals mg	Ovaries mg
1f	36	293	2.06	11.6	0.55	2.33	85.8	99.6
control	37	294	1.99	12.6	0.69	2.25	87.4	92.9
	38	294	1.95	13.5	0.66	2.31	79.4	97.4
	39	287	1.89	12.6	0.74	2.22	61.3	86.9
	40	280	1.89	13.1	0.65	2.42	65.4	89.9
	Mean	289	1.96	12.7	0.66	2.31	75.9	92.9
	sd	6.2	0.073	0.74	0.068	0.078	11.89	5.88
4f	56	286	1.85	13.1	0.60	2.29	88.3	106.7
500	57	280	1.95	14.4	0.58	2.45	75.8	50.8
	58	292	2.06	13.6	0.60	2.42	52.7	111.0
	60	295	1.88	15.1	0.77	2.50	69.2	91.4
	Mean	289	1.93	14.1	0.64	2.42	71.5	90.0
	sd	6.9	0.093	0.86	0.091	0.091	14.83	27.44

sd Standard deviation

## APPENDIX 7

Organ weights - individual values

## Week 3 Recovery (9 June 1995)

Group/ dosage mg/kg/day	Animal no.	Body wt g	Brain			Liver			Spleen			Kidneys			Adrenals			Testes			Seminal Vesicle			Epididymides			
			g	g	g	g	g	g	g	g	g	mg	g	g	g	g	g	g	g	g	g	g	g	g	g	g	
1m	6	418	1.93	16.2	0.84	3.17	53.9	1.417	1.550	0.73	0.436	0.462	0.57														
Control	7	439	2.05	22.2	0.84	3.12	41.2	1.572	1.572	1.17	0.439	0.472	0.68														
	9	413	1.90	19.5	0.70	3.17	61.8	1.357	1.214	1.12	0.420	0.394	0.55														
	10	392	1.88	19.0	0.83	2.51	52.8	0.827	0.829	1.31	0.277	0.289	0.70														
	Mean	415	1.94	19.2	0.80	2.99	52.4	1.293	1.291	1.08	0.393	0.404	0.63														
	sd	19.3	0.075	2.45	0.066	0.324	8.49	0.3238	0.3490	0.247	0.0778	0.0843	0.078														
4m	26	415	2.02	21.1	1.02	3.61	66.5	1.778	1.756	0.93	0.589	0.613	0.85														
500	27	358	2.01	21.4	0.58	2.83	53.1	1.759	1.695	1.57	0.491	0.492	0.82														
	28	426	1.92	21.4	0.73	3.49	61.8	1.754	1.849	1.26	0.541	0.569	1.11														
	29	432	2.10	22.9	0.90	3.75	57.9	1.009	0.900	1.42	0.314	0.274	0.89														
	30	405	1.85	23.3	0.87	3.42	60.8	1.417	1.324	0.68	0.398	0.378	0.76														
	Mean	407	1.98	22.0	0.82	3.42	60.0	1.543	1.505	1.17	0.467	0.465	0.89														
	sd	29.4	0.098	1.02	0.170	0.353	4.95	0.3345	0.3925	0.359	0.1108	0.1392	0.137														

sd Standard deviation

## APPENDIX 7

Organ weights - individual values

Week 5 (26 May 1995)

Group/ dosage mg/kg/day	Animal no.	WT g	Brain g	Liver g	Spleen g	Kidneys g	Adrenals g	Ovaries mg
1f	31	294	2.12	13.9	0.70	2.25	74.6	84.4
Control	32	307	2.02	14.4	0.77	2.73	69.1	86.6
	33	258	1.83	10.1	0.54	2.17	64.7	94.5
	34	244	1.91	11.1	0.60	2.33	60.6	104.3
	35	272	1.88	12.2	0.55	2.42	82.0	119.8
	Mean	275	1.95	12.3	0.65	2.38	70.2	97.9
	sd	25.7	0.117	1.81	0.086	0.218	8.40	14.51
2f	41	260	1.91	11.1	0.74	1.86	81.5	80.1
15	42	261	1.79	12.1	0.60	2.07	82.8	128.7
	43	286	2.02	12.9	0.65	2.35	79.2	92.7
	44	278	1.93	14.3	0.79	2.51	64.6	89.1
	45	279	1.79	13.3	0.62	2.28	80.0	110.8
	Mean	273	1.89	12.7	0.68	2.21	77.6	100.3
	sd	11.6	0.097	1.18	0.080	0.253	7.41	19.42
3f	46	264	1.83	12.0	0.60	2.01	78.8	107.6
150	47	236	1.93	12.4	0.57	2.30	87.1	92.1
	48	293	1.88	15.5	0.71	2.42	60.2	94.3
	49	278	1.95	13.2	0.66	2.24	75.8	90.9
	50	259	1.82	12.2	0.68	2.20	69.6	94.9
	Mean	262	1.88	13.1	0.64	2.24	74.3	96.0
	sd	23.8	0.056	1.44	0.057	0.149	10.09	6.71
4f	51	305	1.76	18.1	0.75	2.73	86.9	117.5
200	52	272	1.86	16.0	0.59	2.49	64.9	80.0
	53	243	1.91	15.0	0.68	1.99	58.7	94.6
	54	264	1.83	17.7	0.62	2.31	83.1	125.6
	55	261	1.77	16.8	0.69	2.29	62.2	86.9
	Mean	269	1.82	16.7	0.67	2.36	71.2	100.9
	sd	22.7	0.063	1.27	0.063	0.274	12.89	19.74

sd Standard deviation

## APPENDIX 7

## Organ weights - individual values

Group/ dosage mg/kg/day	Animal no.	Body wt g	Brain g	Liver g	Spleen g	Kidneys g	Adrenals mg	Testes Left g	Testes Right g	Vesicle Left g	Vesicle Right g	Seminal g	Epididymides g	Prost- ate g	
1m Control	1	380	1.81	16.0	0.70	2.58	46.6	1.707	1.767	0.63	0.388	0.412	0.74		
	2	412	2.08	20.0	0.82	3.38	47.9	1.633	1.402	1.08	0.409	0.413	0.62		
	3	396	1.99	18.9	0.74	3.29	52.4	1.645	1.678	1.33	0.513	0.493	0.66		
	4	369	1.97	21.2	0.74	3.33	62.0	1.544	1.532	0.95	0.434	0.444	0.80		
	5	357	1.93	20.3	0.60	2.61	56.9	1.660	1.633	0.73	0.371	0.372	0.80		
	Mean	383	1.96	19.3	0.72	3.04	53.2	1.594	1.602	0.95	0.423	0.427	0.73		
	sd	22.1	0.099	1.99	0.080	0.404	6.39	0.1071	0.1404	0.279	0.0556	0.0450	0.082		
2m 15	11	380	1.97	20.3	0.80	2.73	60.8	1.675	1.685	1.33	0.533	0.509	0.78		
	12	374	2.06	17.7	0.76	2.89	50.1	1.699	1.656	0.79	0.335	0.376	0.84		
	13	363	1.86	15.4	0.82	2.66	45.5	1.535	1.523	0.73	0.404	0.389	0.77		
	14	430	1.95	19.9	0.96	3.52	57.1	1.157	1.162	0.88	0.430	0.350	0.85		
	15	361	2.00	17.2	0.76	2.85	47.1	1.797	1.783	1.26	0.481	0.501	0.78		
	Mean	382	1.97	18.1	0.82	2.93	52.1	1.579	1.562	1.00	0.437	0.425	0.80		
	sd	28.3	0.075	2.01	0.083	0.344	6.58	0.2497	0.2420	0.282	0.0753	0.0744	0.038		
3m 150	16	349	1.86	19.1	0.60	2.78	46.0	1.139	1.129	1.14	0.386	0.363	0.59		
	17	406	1.94	23.1	0.87	3.50	48.3	1.891	1.826	0.79	0.446	0.405	0.76		
	18	355	1.87	19.9	0.73	3.10	50.2	1.556	1.103	0.89	0.428	0.318	0.77		
	19	408	1.89	27.0	0.76	3.68	62.4	1.084	1.012	1.09	0.325	0.294	0.67		
	20	372	1.84	19.7	0.65	2.75	55.5	1.601	1.606	0.90	0.419	0.434	0.91		
	Mean	377	1.88	21.8	0.72	3.16	52.5	1.454	1.335	0.96	0.401	0.363	0.74		
	sd	27.3	0.060	3.30	0.105	0.419	6.56	0.3388	0.3589	0.149	0.0476	0.0583	0.121		
4m 500	21	380	1.96	27.9	0.76	3.90	56.1	1.260	1.116	1.33	0.352	0.412	0.90		
	22	357	1.79	23.6	0.72	3.12	56.2	1.446	1.349	1.08	0.385	0.362	0.66		
	23	340	1.87	25.0	0.56	3.00	43.9	1.718	1.752	0.85	0.461	0.447	0.64		
	24	381	1.97	26.6	0.74	3.08	52.4	1.702	1.754	0.60	0.438	0.456	0.77		
	25	354	1.81	24.1	0.72	3.17	62.4	1.287	1.268	1.19	0.406	0.444	0.86		
	Mean	362	1.88	25.4	0.72	3.25	54.2	1.483	1.448	1.01	0.408	0.424	0.77		
	sd	17.5	0.082	1.76	0.037	0.366	6.79	0.2195	0.2909	0.287	0.0429	0.0385	0.115		

sd Standard deviation

## Urinalysis - individual values

## Week 3 Recovery (7 June 1995)

Group/	Animal	pH
1f	36	6.4
Control	37	6.6
	38	6.8
	39	6.5
	40	6.1
	Mean	6.5
	sd	0.26
4f	56	6.0
500	57	6.2
	58	6.1
	60	6.0
	Mean	6.1
	sd	0.10

sd Standard deviation

## (Urinalysis - continued)

Week 5 (24 May 1995)

Group/ dosage mg/kg/day	Animal no.	vol- ume ml	pH	SG	Pro- tein mg/dl	TRS	Glu- cose	Ket- ones	Bile pig- ments	Haem- ogen ogens	Microscopy				
											E	P	M	R	O
1f	31	6.0	6.1	1044	78	0	0	0	0	0	0	1	0	0	0
Control	32	5.1	6.1	1040	66	0	0	0	0	0	0	1	0	0	0
	33	5.0	6.2	1038	64	0	0	0	0	0	0	1	0	0	0
	34	5.2	6.1	1037	63	0	0	0	0	0	0	0	1	0	0
	35	5.0	5.9	1046	70	0	0	0	0	0	0	0	2	0	0
	Mean	4.9	6.1	1041	68							1	0	1	0
	sd	1.11	0.11	3.9	6.1							0	0	1	0
2f	41	3.7	6.4	1037	78	0	0	0	0	0	0	0	0	1	0
15	42	5.9	6.3	1033	69	0	0	0	0	0	0	1	0	1	0
	43	3.0	6.1	1037	63	0	0	0	0	0	0	1	0	0	0
	44	7.3	6.2	1031	54	0	0	0	0	0	0	0	1	0	0
	45	5.2	6.0	1036	66	0	0	0	0	0	0	0	1	0	0
	Mean	5.0	6.2	1035	64								0	1	0
	sd	1.72	0.16	2.7	8.9								0	1	0
3f	46	4.1	6.1	1042	73	0	0	0	0	0	0	0	0	2	0
150	47	2.4	5.9	1040	96	+	0	0	0	0	0	1	0	0	0
	48	8.1	6.5	1027	61	0	0	0	0	0	0	0	0	2	0
	49	3.1	5.7	1047	85	+	0	0	0	0	0	0	0	1	0
	50	2.3	5.8	1045	83	++	0	0	0	0	0	0	0	1	0
	Mean	4.0	6.0	1040	80									1	0
	sd	2.40	0.32	7.9	13.2										0
4f	51	7.0	5.8	1036	66	0	0	0	0	0	0	1	0	0	0
500	52	3.9	5.8	1045	76	0	0	0	0	0	1	0	0	1	0
	53	5.8	5.8	1040	63	0	0	0	0	0	0	0	0	1	0
	54	3.0	5.7	1072	86	++	0	0	0	0	0	1	0	0	0
	55	5.2	5.6	1038	63	++	0	0	0	0	0	1	0	0	0
	Mean	5.0	5.7	1046	71								1	0	1
	sd	1.57	0.09	14.8	10.0										0

sd Standard deviation

## APPENDIX 6

## Urinalysis - individual values

Week 5 (24 May 1995)

Group/ dosage mg/kg/day	Animal no.	Vol- ume ml	pH	SG	Pro- tein mg/dl	TRS	Ket- one	Bile pig- ments	Haem pig- ments	Microscopy					
										E	P	M	R	O	C
1m control	1	6.0	6.0	1038	120	0	0	TR	0	0	0	0	1	0	0
	2	5.9	6.4	1038	128	+	0	TR	0	0	0	0	0	1	0
	3	3.1	6.0	1064	502	+	0	0	0	0	0	0	0	1	2SP
	4	3.9	6.4	1035	134	+	0	TR	0	0	0	0	0	0	2SP
	5	5.0	6.3	1034	146	0	0	0	0	0	0	0	0	2	0
	Mean	4.8	6.2	1042	206									1	0
	sd	1.26	0.20	12.5	165.7									0	0
2m 15	11	5.2	6.1	1039	390	0	0	0	0	0	0	0	0	1	0
	12	4.9	6.0	1043	139	TR	0	TR	0	0	0	1	0	0	0
	13	3.4	6.2	1044	409	+	0	TR	0	0	0	0	0	2	0
	14	8.0	6.0	1035	109	+	0	0	0	0	0	0	0	1	0
	15	5.3	6.0	1047	468	++	0	0	0	0	0	0	0	1	0
	Mean	5.4	6.1	1042	303									1	0
	sd	1.66	0.09	4.7	166.3									0	0
3m 150	16	5.1	6.3	1033	123	0	0	TR	0	0	0	0	0	2	0
	17	4.0	6.2	1045	389	0	0	TR	0	0	0	0	0	2	0
	18	6.4	6.5	1040	140	0	0	TR	0	0	0	0	0	2	0
	19	7.5	6.4	1040	449	TR	0	0	0	0	0	1	0	1	0
	20	3.4	6.9	1072	538	TR	0	0	0	0	0	1	0	2	0
	Mean	5.3	6.5	1046	328									2	0
	sd	1.69	0.27	15.1	187.0									0	0
4m 500	21	5.0	6.0	1048	420	++	0	0	0	0	1	0	0	1	0
	22	12.0	6.6	1030	117	0	0	TR	0	0	1	0	0	1	6
	23	3.1	5.9	1068	554	0	0	TR	0	0	0	0	0	0	1SP
	24	7.2	6.0	1048	179	++	0	TR	0	0	0	0	0	2	0
	25	5.3	6.1	1043	139	+++	0	TR	0	0	0	0	0	0	2SP
	Mean	6.5	6.1	1047	282									1	0
	sd	3.39	0.28	13.7	194.5									0	0

sd Standard deviation